I.2	Cancer medicines for children – Langerhans cell histiocytosis – EMLc
Draft recommendation	☐ Recommended ☒ Not recommended **Justification:** The application is requesting the following: • As a new entity for Langerhans cell histiocytosis with existing medicine on the WHO EMLc 2021 for cytarabine, human/normal immunoglobuline, 6-mercaptopurine, methotrexate, prednisone, vincristine, vinblastine. • As a new individual medicine for cladribine (2-CdA) However, LCH is a rare disease and does not fall under the definition of essential. There should be other pathways that look at use of medicines for rare diseases.
Does the proposed medicine address a relevant public health need?	☒ Yes ☐ No ☐ Not applicable **Comments:** The disease is more common in children than adults. It occurs in about one out of every 200,000 children. The application reports that the annual incidence of LCH is 4.6 cases per 1 million children under 15 years of age. Another study indicates that Langerhans cell histiocytosis (LCH) affects 5–9 in 10^6 children younger than 15 years and 1 in 10^6 older patients.[1] Thus, it can be classified as a rare disease (according to FDA definitions).

[1] Raciborska, A., Bilska, K., Węcławek-Tompol, J. et al. Clinical characteristics and outcome of pediatric patients diagnosed with Langerhans cell histiocytosis in pediatric hematology and oncology centers in Poland. BMC Cancer 20, 874 (2020). https://doi.org/10.1186/s12885-020-07366-3

Does adequate evidence exist for the efficacy/effectiveness of the medicine for the proposed indication? (this may be evidence included in the application, and/or additional evidence identified during the review process)	☐ Yes ☒ No ☐ Not applicable **Comments:** For those medicines for which a new indication has been requested (cytarabine, human/normal immunoglobuline, 6-mercaptopurine, methotrexate, prednisone, vincristine, vinblastine), these have already been listed on the EMLc, and their use in LCH has been as per protocol development over time (as stated in the application). LCH treatment protocols have been developed over the last few decades. The application indicates that the currently used LCH IV protocol is a result from findings and improvements of previous protocol versions, and the medicines used in the 80s' to treat LCH (vinblastine, doxorubicin, etoposide, vincristine, cyclophosphamide, prednisone) mainly consisted of the medicines still used today (vinblastine, vincristine, cyclophosphamide, prednisone, cytarabine, cladribine, methotrexate, 6-mercaptopurine). The application does state that due to the long-standing experience with these drug combinations, no studies examined the effect of the individual medicines for the treatment of LCH. The activity and toxicity of 2-CDA is still being investigated in a current LCH-IV treatment protocol for pediatric patients with LCH, and other studies indicate some success as monotherapy and then in combination with other agents.
Does adequate evidence exist for the safety/harms associated with the proposed medicine? (this may be evidence included in the application, and/or additional evidence identified during the review process)	☒ Yes ☐ No ☐ Not applicable **Comments:** For those medicines for which a new indication has been requested (cytarabine, human/normal immunoglobuline, 6-mercaptopurine, methotrexate, prednisone, vincristine, vinblastine), these have already been listed on the EMLc, and safety profiles have been reviewed previously. For ***cladribine***: Data from hairy cell leukemia studies showed that about 70% of people taking the drug developed dangerously low levels of white blood cells and about 30% developed infections and some of those progressed to septic shock; about 40% of people taking the drug had fewer red blood cells and became severely anaemic; and about 10% of people had too few platelets. At the dosage used to treat hairy cell leukemia in two clinical trials, 16% of people had rashes and 22% had nausea, the nausea generally did not lead to vomiting.[2]
Are there any adverse effects of concern, or that may require special monitoring?	☒ Yes ☐ No ☐ Not applicable **Comments:** For cladribine: The most clinically relevant adverse reactions were lymphopenia and herpes zoster. The use of cladribine tablets is contraindicated in pregnant women, and women of childbearing potential must use effective contraception to prevent pregnancy during treatment and 6 months after receiving the last dose.

[2] https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=a2592a9b-bca6-4a5a-89c2-855a0634d5fe

Are there any special requirements for the safe, effective and appropriate use of the medicines? (e.g. laboratory diagnostic and/or monitoring tests, specialized training for health providers, etc)	☒ Yes ☐ No ☐ Not applicable **Comments:** Some of the medications are IV/IMI administered and therefore require skilled personnel for administration. Diagnostic capabilities are required as are skills in identifying the condition and managing side effects and toxicities.
Are there any issues regarding cost, cost-effectiveness, affordability and/or access for the medicine in different settings?	☒ Yes ☒ No ☐ Not applicable **Comments:** All the medicines that are already listed on the EMLc are available in generic form. Cladribine has no generic alternative.
Are there any issues regarding the registration of the medicine by national regulatory authorities? (e.g. accelerated approval, lack of regulatory approval, off-label indication)	☐ Yes ☒ No ☐ Not applicable **Comments:** For those medicines for which a new indication has been requested (cytarabine, human/normal immunoglobuline, 6-mercaptopurine, methotrexate, prednisone, vincristine, vinblastine), these are available in countries in generic form as well. Cladribine tablets were approved in Europe, in August 2017, for highly active relapsing-remitting multiple sclerosis, and has since been approved by the FDA for the treatment of relapsing-remitting and secondary progressive multiple sclerosis in the US. The product has been registered in more than 80 countries globally.
Is the proposed medicine recommended for use in a current WHO guideline? (refer to: https://www.who.int/publications/who-guidelines)	☒ Yes ☒ No ☐ Not applicable **Comments:** For those medicines for which a new indication has been requested (cytarabine, human/normal immunoglobuline, 6-mercaptopurine, methotrexate, prednisone, vincristine, vinblastine), these have already been listed on the EMLc for other conditions. Cladribine tablets is a new addition requested for this specific indication.